REMARKS

Claims 1 to 9 and 14 to 25 are in the application. Claims 10-12 have been cancelled. Claims 19 to 25 have been added. Claims 1, 2, 3, 7 and 15 have been amended. Support for the amendments lie in the claims as originally filed, in the specification in the working examples or on page 5, lines 10 to 18. No new matter is believed added. Applicants reserve their right to file divisional applications on all cancelled or deleted subject matter.

Claims 1 to 12 and 14 to 18 have been made the subject of a restriction requirement under 35 USC §121 and the groups are as indicated in the outstanding office action.

Applicants confirm their election of Group I, and the election as a species of the compound of Example 1 as so indicated on pages 3 and 4 of the Office Action. Applicants respectfully traverse the restriction as between method of using and method of preparation as all of these are related by the compounds themselves, which result from a common research effort. Re-joinder of the process claims is respectfully requested upon allowance of the compound claims.

Applicants enclose herewith the latest responses from their co-pending applications USSN 10/522,955 and USSN 10/587,790 for the Examiners convenience.

Rejection under 35 USC §112

Claim 7 is rejected under 35 USC §112, 2nd paragraph as being indefinite. Applicants respectfully traverse this rejection.

Claim 7 utilizes terminology which is commonly found in European based application that refers to Examples within the specification. There is nothing indefinite about the compounds of Examples 1 to 9. They are clear and concise as to what has been made. However, in order to advance prosecution on the merits, Claim 7 has been amended to correspond to US practice.

Therefore in view of these amendments and remarks, reconsideration and withdrawal of the rejection to Claim 7 under 35 USC §112, 2nd paragraph is respectfully requested.

Rejection under 35 USC §112

Claims 1-11 and 15-18 are rejected under 35 USC §112, first paragraph, because "the specification, while being enabling for compounds of formula (I), a pharmaceutically acceptable salt of a compound of formula (I), as well as carbamates and amide derivatives of compounds of formula (I), does not reasonably provide enablement for pharmaceutically acceptable derivatives … that are not pharmaceutically acceptable salts, carbamates or amides of a compound of formula (I)." Applicants respectfully traverse this rejection.

Applicants do not agree with the Examiner's arguments on developability or predictability et al., as recited in the Office Action, pages 6 to 10, with respect to the instant compounds. However, in order to advance prosecution on the merits the claims have been amended to recite "pharmaceutically acceptable salt".

Therefore in view of these amendments and remarks, reconsideration and withdrawal of the rejection to Claims 1-11 and 15-18 under 35 USC §112, 2nd paragraph is respectfully requested.

Rejection under 35 USC 103(a)

Claims 1-11 and 15-18 are rejected under 35 USC §103(a) as being unpatentable over US Patent publication US2006/0122221, Angell et al. (herein after'221) in view of WO 03/097610, Brill et al. (herein after '610). Applicants respectfully traverse this rejection.

Applicant's '221 application as noted by the Examiner discloses compounds wherein the "A" ring is a diazole. However, in those instances when the A ring is a diazole, the substitutable group on the "A" ring is attached through a ketone or an $S(O)_2$ moiety, and not directly to the heterocyclic ring, or through a carbon chain linkage as claimed herein. The '221 application also does not provide for a carbon chain linkage to the heterocyclic ring as in the present invention, e.g. a -(CH2)m- heterocyclic.

When a heterocyclic ring, such as the elected tetrahydrofuran ring is attached in the present invention there is no ketone or S(O)2 linkage. The group is attached either directly, or through a carbon chain.

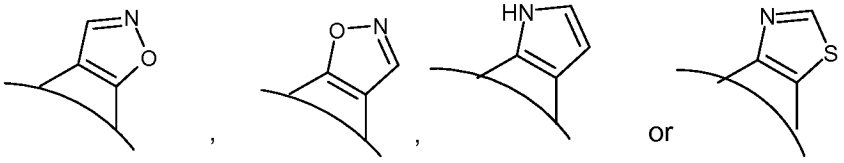
The '221 publication teaches a wide range of substituent on the A ring as shown below from paragraph 0004 of the '221 publication:

[0004] A is a fused 5-membered heteroaryl ring optionally substituted by up to two substituents independently selected from C_{1-6}alkyl, $-(CH_2)_m-C_{3-7}$cycloalkyl, halogen, cyano, trifluoromethyl, $-(CH_2)_mOR^3$, $-(CH_2)_mCO_2R^3$, $-(CH_2)_mNR^3R^4$, $-(CH_2)_mCONR^3R^4$, $-(CH_2)_mNHCOR^3$, $-(CH_2)_mSO_2NR^3R^4$, $-(CH_2)_mNHSO_2R^3$, $-(CH_2)_mSO_2(CH_2)_nR^5$, a 5- or 6-membered heterocyclyl ring containing nitrogen optionally substituted by C_{1-2}alkyl or $-(CH_2)_mCO_2R^3$, and a 5-membered heteroaryl ring optionally substituted by C_{1-2}alkyl:

The substitution is a 5- or 6- membered heterocyclic ring containing a nitrogen optionally substituted by a C_{1-2} alkyl or a $(CH_2)mC(O)_2R$ moiety is only one of many optional substituents to select from in the recited list of groups. This moiety, the 5- or 6- membered heterocyclic ring containing a nitrogen is further described in paragraphs 0057 and 0058 of the '221 publication as a 4-piperidinyl, or a piperazinyl.

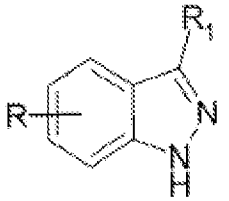
The '221 publication does not describe nor suggest substitution of the A ring by an optionally substituted tetrahydrofuranyl, tetrahydropyranyl or morpholinyl ring, e.g. a –(CH2)m heterocyclic ring containing 1 or 2 heteroatoms independently selected from oxygen, or sulfur, or a ring of oxygen and nitrogen heteroatoms. Consequently, there is no motivation to direct the skilled artisan to instead substitute the diazole "A" ring by such groups. Claim 1 has been amended to recite that the heterocyclic ring in the $-(CH_2)_m$heterocyclic moiety is a tetrahydrofuranyl, tetrahydropyranyl or morpholinyl ring.

It should also be noted (as shown in the responses submitted to the USPTO during prosecution of USSN 10/522,955 (the '221) application), that the claims have been amended to recite the A ring as a fused 5-membered heteroaryl ring selected from:



Consequently there is no motivation to pick and choose from the list of substitutions available on the "A" ring a heterocyclic 5 or 6 membered nitrogen containing ring, nor specifically to pick the "A" ring as a diazole with such substitution.

Brill teaches compounds of the formula:



(I)

wherein, *inter alia*

R is, in position 5 or 6 of the indazole ring, a halogen atom or an optionally substituted group selected from straight or branched C_2-C_6 alkenyl, C_2-C_6 alkynyl, or aryl with from 0 to 3 heterostoms selected from S, O and N;

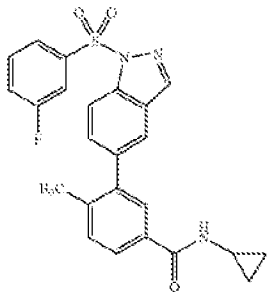
R_1 is an optionally substituted group selected from

-N=CH-NR_aR_b, -NHCOR', -NHCONR'R", -$NHSO_2$R' or -NHCOOR';

The R_1 moiety is in the 3-position of the ring but contrary to the Examiners comments on page 12 of the Office Action, substitution of the 3-position is not by a tetrahydrofuran ring. The 3-position is always substituted by a nitrogen and more specifically through a group which is: -N=CH-NR_aR_b, -NHCOR', -NHCONR'R", -$NHSO_2$R' or -NHCOOR';

That is not the same as the elected invention herein. It is also not necessary in Applicants invention to substitute through the 3-position which is required by Brill et al. in the '610 application. Applicants do not require linkage of the -$(CH_2)_m$heterocyclyl moiety to the diazole ring through a group such as taught in Brill et al., e.g. a -N=CH-NR_aR_b, -NHCOR', -NHCONR'R", -$NHSO_2$R' or -NHCOOR';

In contrast to Brill et al., Applicant's '221 application also does not substitute on the 3-position but substitutes directly onto the ring nitrogen of the diazole ring, as shown herein by Example 19 and the two examples as illustrated by the Examiner on page 11 of the office action.



Consequently, there is no suggestion or motivation to direct the skilled artisan to utilize the teachings of Brill et al. to make compounds of the present invention.

Consequently in view of these remarks and amendments reconsideration and withdrawal of the rejection to the claims under 35 USC §103 is respectfully requested.

Double Patenting

Claims 1-11 and 15-18 are provisionally rejected on the ground of non-statutory double patenting over claims 1-13 and 19-23 of copending application USSN 10/587,790. Applicants respectfully traverse this rejection.

Applicants copending application USSN 10/587,790 is directed to an "A" ring which is substituted by a $-(CH_2)_m$aryl or $-(CH_2)_m$heteroaryl ring. Both applications are filed on the same day.

From page 6 of the corresponding published PCT application (WO2005/073189) the substituents $-(CH_2)_m$aryl or $-(CH_2)_m$heteroaryl ring are described as:

> In one embodiment, the $-(CH_2)_m$aryl group is $-(CH_2)_m$phenyl.
>
> In one embodiment, the $-(CH_2)_m$heteroaryl group is a group wherein the heteroaryl is a 5- or 6-membered heteroaryl ring containing up to two heteroatoms independently selected from oxygen, nitrogen and sulfur. In a further embodiment, the $-(CH_2)_m$heteroaryl group include groups wherein the heteroaryl is a 5- or 6-membered heteroaryl ring containing up to two heteroatoms independently selected from oxygen and nitrogen, for example pyridyl, isoxazolyl, pyrazolyl, imidazolyl, pyrimidinyl or pyrazinyl. Representative examples of the $-(CH_2)_m$heteroaryl group include groups wherein the heteroaryl is a 5- or 6-membered heteroaryl ring containing up to two heteroatoms independently selected from oxygen and nitrogen, for example pyridyl, isoxazolyl or pyrimidinyl. Further representative examples of the $-(CH_2)_m$heteroaryl group include groups wherein the heteroaryl is a 5- or 6-membered heteroaryl ring containing up to two heteroatoms independently selected from oxygen and nitrogen, for example pyrazolyl, imidazolyl or pyrazinyl.

In no instance is the $-(CH_2)_m$heteroaryl or $-(CH_2)_m$ aryl ring a tetrahydrofuranyl, tetrahydropyranyl or morpholinyl ring.

The Examiner comments on page 14 of the office action, 2nd ¶ that "Furthermore, there is no apparent reason why applicant would be prevented from presenting claims corresponding to those of the instant application in the other copending application".

This is clearly incorrect. There is no description of a $-(CH_2)_m$heterocyclic ring in the USSN 10/587,790 for which a claim could be made. Nor is there a suitable description in

the instant application to provide for substitution of the "A" ring by a -$(CH_2)_m$heteroaryl or -$(CH_2)_m$ aryl ring.

The subject matter of each application is independent and distinct from the subject matter of the other. The Examiner is requested to provide the basis for this statement in detail so that it may properly be responded to.

In view of these remarks, withdrawal of the obvious type double patenting is respectfully requested.

CONCLUSION

Should the Examiner have any questions or wish to discuss any aspect of this case, the Examiner is encouraged to call the undersigned at the number below. If any additional fees or charges are required by this paper, the Commissioner is hereby authorized to charge Deposit account 19-2570 accordingly.

Respectfully submitted,

/ /

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Angell et al.	16 January 2009
Serial No.:	10/522,955	Group Art Unit: 1626
Filed:	14 November 2005	Examiner: M. Barker
For:	Fused Heteroaryl Derivatives for Use As p38 Kinase Inhibitors (As Amended)	

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE

Sir:

Applicants now respond to the Office Action of 19 November 2008, and respectfully request entry of the following Remarks and Amendments into the record.

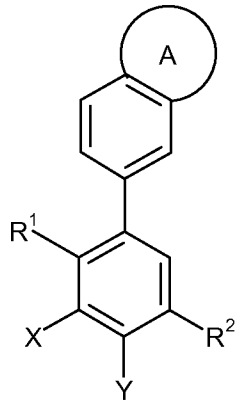
Amendments to the Claims are reflected in the listing of claims, which begins on page 2 of this paper.

Remarks/Arguments begin on page 14 of this paper.

Amendments to the claims

This listing of claims will replace all prior versions, and listings, of claims in the application:

1 (currently amended). A compound of formula (I):



(I)

wherein

A is a fused 5-membered heteroaryl ring selected from an isoxazolyl ring, a pyrrolyl or a thiazolyl ring, which ring is optionally substituted by up to two substituents independently selected from C_{1-6}alkyl, -$(CH_2)_m$-C_{3-7}cycloalkyl, halogen, cyano, trifluoromethyl, -$(CH_2)_mOR^3$, -$(CH_2)_mCO_2R^3$, -$(CH_2)_mNR^3R^4$, -$(CH_2)_mCONR^3R^4$, -$(CH_2)_mNHCOR^3$, -$(CH_2)_mSO_2NR^3R^4$, -$(CH_2)_mNHSO_2R^3$, -$(CH_2)_mSO_2(CH_2)_nR^5$, a 5- or 6-membered heterocyclyl ring containing nitrogen optionally substituted by C_{1-2}alkyl or -$(CH_2)_mCO_2R^3$, and a 5-membered heteroaryl ring optionally substituted by C_{1-2}alkyl;

R^1 is selected from methyl and chloro;

R^2 is selected from -NH-CO-R^6 and -CO-NH-$(CH_2)_q$-R^7;

R^3 is selected from hydrogen, C_{1-6}alkyl optionally substituted by up to two OH groups, -$(CH_2)_m$-C_{3-7}cycloalkyl, -$(CH_2)_m$phenyl optionally substituted by R^8 and/or R^9 and -$(CH_2)_m$heteroaryl optionally substituted by R^8 and/or R^9 [[,]];

R^4 is selected from hydrogen and C_{1-6}alkyl, or

R^3 and R^4, together with the nitrogen atom to which they are bound, form a 5- or 6-membered heterocyclic ring optionally containing one additional heteroatom selected from oxygen, sulfur and N-R^{10};

R^5 is selected from C_{1-6}alkyl optionally substituted by up to three halogen atoms, C_{2-6}alkenyl optionally substituted by phenyl, C_{3-7}cycloalkyl, heteroaryl optionally substituted by up to three R^8 and/or R^9 groups, and phenyl optionally substituted by R^8 and/or R^9;

R^6 is selected from hydrogen, C_{1-6}alkyl, $-(CH_2)_q$-C_{3-7}cycloalkyl, trifluoromethyl, $-(CH_2)_r$heteroaryl optionally substituted by R^{11} and/or R^{12}, and $-(CH_2)_r$phenyl optionally substituted by R^{11} and/or R^{12};

R^7 is selected from hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, $-CONHR^{13}$, phenyl optionally substituted by R^{11} and/or R^{12}, and heteroaryl optionally substituted by R^{11} and/or R^{12};

R^8 and R^9 are each independently selected from halogen, cyano, trifluoromethyl, nitro, C_{1-6}alkyl, C_{1-6}alkoxy, $-CONR^{13}R^{14}$, $-COR^{15}$, $-CO_2R^{15}$, and heteroaryl, or

R^8 and R^9 are linked to form a fused 5-membered heterocyclyl ring containing one heteroatom selected from oxygen, sulphur and N-R^{10}, or a fused heteroaryl ring;

R^{10} is selected from hydrogen and methyl;

R^{11} is selected from C_{1-6}alkyl, C_{1-6}alkoxy, $-(CH_2)_q$-C_{3-7}cycloalkyl, $-CONR^{13}R^{14}$, $-NHCOR^{14}$, halogen, CN, $-(CH_2)_sNR^{16}R^{17}$, trifluoromethyl, phenyl optionally substituted by one or more R^{12} groups, and heteroaryl optionally substituted by one or more R^{12} groups;

R^{12} is selected from C_{1-6}alkyl, C_{1-6}alkoxy, halogen, trifluoromethyl, and $-(CH_2)_sNR^{16}R^{17}$;

R^{13} and R^{14} are each independently selected from hydrogen and C_{1-6}alkyl, or

R^{13} and R^{14}, together with the nitrogen atom to which they are bound, form a 5- or 6-membered heterocyclic ring optionally containing one additional heteroatom selected from oxygen, sulfur and N-R^{10}, wherein the ring may be substituted by up to two C_{1-6}alkyl groups;

R^{15} is C_{1-6}alkyl;

R^{16} is selected from hydrogen, C_{1-6}alkyl and $-(CH_2)_q$-C_{3-7}cycloalkyl optionally substituted by C_{1-6}alkyl,

R^{17} is selected from hydrogen and C_{1-6}alkyl, or

R^{16} and R^{17}, together with the nitrogen atom to which they are bound, form a 5- or 6-membered heterocyclic ring optionally containing one additional heteroatom selected from oxygen, sulfur and N-R^{10};

X and Y are each independently selected from hydrogen, methyl and halogen;

m is selected from 0, 1, 2 and 3;

n is selected from 0, 1, 2 and 3;

q is selected from 0, 1 and 2;

r is selected from 0 and 1; and

s is selected from 0, 1, 2 and 3.

2 (currently amended). A compound according to claim 1 wherein A is ~~a fused 5-membered heteroaryl ring containing up to two heteroatoms independently selected from oxygen and nitrogen~~ optionally substituted by up to two substituents independently selected from C_{1-4}alkyl, $-(CH_2)_m-C_{3-7}$cycloalkyl, $-(CH_2)_mCO_2R^3$, $-(CH_2)_mNR^3R^4$, $-(CH_2)_mCONR^3R^4$, $-(CH_2)_mNHCOR^3$, $-(CH_2)_mSO_2(CH_2)_nR^5$, and a 5- or 6-membered heterocyclyl ring containing nitrogen optionally substituted by C_{1-2}alkyl or $-(CH_2)_mCO_2R^3$.

3 (previously presented). A compound according to claim 1 wherein R^1 is methyl.

4 (previously presented). A compound according to claim 1 wherein R^2 is $-CO-NH-(CH_2)_q-R^7$.

5 (previously presented). A compound according to claim 1 wherein X is hydrogen or fluorine.

6 (Previously presented). A compound according to claim 1 which is:

N-Cyclopropyl-4-methyl-3-(3-piperidin-4-yl-1,2-benzisoxazol-6-yl)benzamide;

4-Methyl-N-(3-morpholin-4-ylphenyl)-3-(3-piperidin-4-yl-1,2-benzisoxazol-6-yl)benzamide;

N-[4-Methyl-3-(3-piperidin-4-yl-1,2-benzisoxazol-6-yl)phenyl]-2-pyrrolidin-1-ylisonicotinamide;

N-[4-Methyl-3-(3-methyl-1,2-benzisoxazol-6-yl)phenyl]-2-pyrrolidin-1-ylisonicotinamide;

N-[4-Methyl-3-(3-methyl-1,2-benzisoxazol-6-yl)phenyl]thiophene-3-carboxamide;

N-[4-Methyl-3-(3-methyl-1,2-benzisoxazol-6-yl)phenyl]-3-furamide;

4-Methyl-3-(3-methyl-1,2-benzisoxazol-6-yl)-N-(3-morpholin-4-ylphenyl)benzamide;

4-Methyl-3-(3-methyl-1,2-benzisoxazol-6-yl)-N-(1,3-thiazol-2-yl)benzamide;

N-Cyclopropyl-4-methyl-3-(3-methyl-1,2-benzisoxazol-6-yl)benzamide;

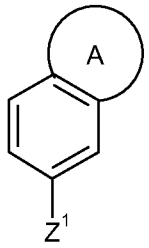
or a pharmaceutically acceptable salt thereof.

7 (previously presented). A pharmaceutical composition comprising a compound according to claim 1 in admixture with one or more pharmaceutically acceptable carriers, diluents or excipients.

8. and 9. (Cancelled)

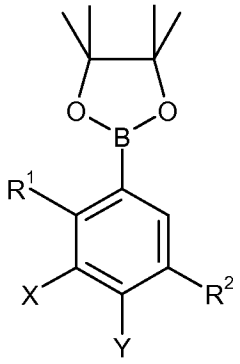
10 (previously presented). A process for preparing a compound of formula (I) according to claim 1 which comprises

(a) reacting a compound of formula (II)

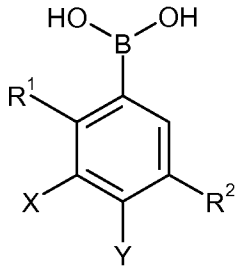


(II)

in which A is defined in claim 1 and Z^1 is halogen,
with a compound of formula (IIIA) or (IIIB)



(IIIA)

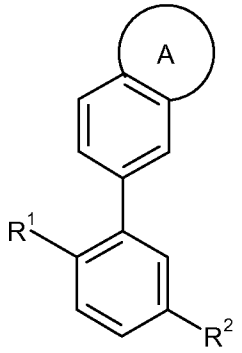


(IIIB)

in which R^1, R^2, X and Y are as defined in claim 1,
in the presence of a catalyst, or

(b) final stage modification of one compound of formula (I) as defined in claim 1 to give another compound of formula (I) as defined in claim 1.

11 (currently amended). A compound of formula (IA):



(IA)

wherein

A is a fused 5-membered heteroaryl ring selected from an isoxazolyl ring, a pyrrolyl or a thiazolyl ring, which ring is optionally substituted by up to two substituents independently selected from C_{1-6}alkyl, $-(CH_2)_m-C_{3-7}$cycloalkyl, halogen, cyano, trifluoromethyl, $-(CH_2)_mOR^3$, $-(CH_2)_mNR^3R^4$, $-(CH_2)_mCONR^3R^4$, $-(CH_2)_mNHCOR^3$, $-(CH_2)_mSO_2NR^3R^4$, $-(CH_2)_mNHSO_2R^3$, $-(CH_2)_mSO_2(CH_2)_nR^5$, a 5- or 6-membered heterocyclyl ring containing nitrogen optionally substituted by C_{1-2}alkyl and a 5-membered heteroaryl ring optionally substituted by C_{1-2}alkyl;

R^1 is selected from methyl and chloro;

R^2 is selected from $-NH-CO-R^6$ and $-CO-NH-(CH_2)_q-R^7$;

R^3 is selected from hydrogen, C_{1-6}alkyl optionally substituted by up to two OH groups, $-(CH_2)_m-C_{3-7}$cycloalkyl, $-(CH_2)_m$phenyl optionally substituted by R^8 and/or R^9 and $-(CH_2)_m$heteroaryl optionally substituted by R^8 and/or R^9

R^4 is selected from hydrogen and C_{1-6}alkyl, or

R^3 and R^4, together with the nitrogen atom to which they are bound, form a 5- or 6-membered heterocyclic ring optionally containing one additional heteroatom selected from oxygen, sulfur and N-R^{10};

R^5 is selected from C_{1-6}alkyl, C_{3-7}cycloalkyl, heteroaryl optionally substituted by R^8 and/or R^9, and phenyl optionally substituted by R^8 and/or R^9;

R^6 is selected from hydrogen, C_{1-6}alkyl, -$(CH_2)_q$-C_{3-7}cycloalkyl, trifluoromethyl, -$(CH_2)_r$heteroaryl optionally substituted by R^{11} and/or R^{12}, and -$(CH_2)_r$phenyl optionally substituted by R^{11} and/or R^{12};

R^7 is selected from hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, $CONHR^{13}$, phenyl optionally substituted by R^{11} and/or R^{12}, and heteroaryl optionally substituted by R^{11} and/or R^{12};

R^8 and R^9 are each independently selected from halogen, cyano, trifluoromethyl, C_{1-6}alkyl, C_{1-6}alkoxy, COR^{15} , CO_2R^{15}, and heteroaryl, or

R^8 and R^9 are linked to form a fused 5-membered heterocyclyl ring containing one heteroatom selected from oxygen, sulphur and N-R^{10};

R^{10} is selected from hydrogen and methyl;

R^{11} is selected from C_{1-6}alkyl, C_{1-6}alkoxy, -$(CH_2)_q$-C_{3-7}cycloalkyl, -$CONR^{13}R^{14}$, -$NHCOR^{14}$, halogen, CN, -$(CH_2)_sNR^{16}R^{17}$, trifluoromethyl, phenyl optionally substituted by one or more R^{12} groups, and heteroaryl optionally substituted by one or more R^{12} groups;

R^{12} is selected from C_{1-6}alkyl, C_{1-6}alkoxy, halogen, trifluoromethyl, and -$(CH_2)_sNR^{16}R^{17}$;

R^{13} and R^{14} are each independently selected from hydrogen and C_{1-6}alkyl, or

R^{13} and R^{14}, together with the nitrogen atom to which they are bound, form a 5- or 6-membered heterocyclic ring optionally containing one additional heteroatom selected from oxygen, sulfur and N-R^{10}, wherein the ring may be substituted by up to two C_{1-6}alkyl groups;

R^{15} is C_{1-6}alkyl;

R^{16} is selected from hydrogen, C_{1-6}alkyl and -$(CH_2)_q$-C_{3-7}cycloalkyl optionally substituted by C_{1-6}alkyl,

R^{17} is selected from hydrogen and C_{1-6}alkyl, or

R^{16} and R^{17}, together with the nitrogen atom to which they are bound, form a 5- or 6-membered heterocyclic ring optionally containing one additional heteroatom selected from oxygen, sulfur and N-R^{10};

m is selected from 0, 1, 2 and 3;

n is selected from 0, 1, 2 and 3;

q is selected from 0, 1 and 2;

r is selected from 0 and 1; and

s is selected from 0, 1, 2 and 3.

12 (currently amended). A compound according to claim 1 which is:

N-[4-methyl-3-(3-piperidin-4-yl-1,2-benzisoxazol-6-yl)phenyl]-2-pyrrolidin-1-ylisonicotinamide;

~~N-cyclopropyl-4-methyl-3-[1-(phenylsulfonyl)-1H-indazol-5-yl]benzamide;~~

~~N-cyclopropyl-3-{1-[(3-fluorophenyl)sulfonyl]-1H-indazol-5-yl}-4-methylbenzamide;~~

~~N-cyclopropyl-4-methyl-3-[1-(methylsulfonyl)-1H-indazol-5-yl]benzamide;~~

~~N-cyclopropyl-3-{1-[(4-fluorophenyl)sulfonyl]-1H-indazol-5-yl}-4-methyl benzamide;~~

N -cyclopropyl-4-methyl-3-[3-(4-morpholinyl)-1,2-benzisoxazol-6-yl]benzamide;

N-cyclopropyl-4-methyl-3-{3-[2-oxo-2-(1,3-thiazol-2-ylamino)ethyl]-1,2-benzisoxazol-6-yl}benzamide;

N-cyclopropyl-4-methyl-3-[3-(4-morpholinylmethyl)-1,2-benzisoxazol-6-yl]benzamide;

N-cyclopropyl-4-methyl-3-[3-(1-pyrrolidinylmethyl)-1,2-benzisoxazol-6-yl]benzamide;

~~N-cyclopropyl-4-methyl-3-{1-[(1-methylethyl)sulfonyl]-1H-indazol-5-yl}benzamide);~~

~~N-cyclopropyl-3-[1-(ethylsulfonyl)-1H-indazol-5-yl]-4-methylbenzamide;~~

~~N-cyclopropyl-3-[1-(cyclopropylsulfonyl)-1H-indazol-5-yl]-4-methylbenzamide;~~

~~N-cyclopropyl-4-methyl-3-[1-(2-thienylsulfonyl)-1H-indazol-5-yl]benzamide;~~

~~3-{1-[(2-cyanophenyl)sulfonyl]-1H-indazol-5-yl}-N-cyclopropyl-4-methylbenzamide;~~

~~N-cyclopropyl-3-fluoro-4-methyl-5-[1-(2-thienylsulfonyl)-1H-indazol-5-yl]benzamide;~~

~~N-cyclopropyl-3-fluoro-4-methyl-5-[1-(3-thienylsulfonyl)-1H-indazol-5-yl]benzamide;~~

~~N-cyclopropyl-3-fluoro-4-methyl-5-{1-[(1-methylethyl)sulfonyl]-1H-indazol-5-yl}benzamide;~~

~~N-cyclopropyl-3-fluoro-4-methyl-5-[1-(propylsulfonyl)-1H-indazol-5-yl]benzamide;~~

~~N-cyclopropyl-3-fluoro-4-methyl-5-[1-(methylsulfonyl)-1H-indazol-5-yl]benzamide;~~

~~3-[1-(butylsulfonyl)-1H-indazol-5-yl]-N-cyclopropyl-5-fluoro-4-methylbenzamide;~~

~~N-cyclopropyl-3-[1-(cyclopropylsulfonyl)-1H-indazol-5-yl]-5-fluoro-4-methylbenzamide;~~

~~3-{1-[(5-chloro-2-thienyl)sulfonyl]-1H-indazol-5-yl}-N-cyclopropyl-5-fluoro-4-methylbenzamide;~~

~~N-cyclopropyl-3-{1-[(3,5-dimethyl-4-isoxazolyl)sulfonyl]-1H-indazol-5-yl}-5-fluoro-4-methylbenzamide;~~

~~N-cyclopropyl-3-[1-(ethylsulfonyl)-1H-indazol-5-yl]-5-fluoro-4-methylbenzamide;~~

~~3-{1-[(2-chlorophenyl)sulfonyl]-1H-indazol-5-yl}-N-cyclopropyl-5-fluoro-4-methyl benzamide;~~

~~N-cyclopropyl-3-fluoro-4-methyl-5-{1-[(2-methylphenyl)sulfonyl]-1H-indazol-5-yl}benzamide;~~

~~N-cyclopropyl-3-fluoro-4-methyl-5-[1-(phenylsulfonyl)-1H-indazol-5-yl]benzamide;~~

~~N-cyclopropyl-3-{1-[(2,5-difluorophenyl)sulfonyl]-1H-indazol-5-yl}-5-fluoro-4-methyl benzamide;~~

~~N-cyclopropyl-3-fluoro-5-{1-[(2-fluorophenyl)sulfonyl]-1H-indazol-5-yl}-4-methylbenzamide;~~

~~N-cyclopropyl-3-[1-(cyclopropylmethyl)-1H-indazol-5-yl]-4-methylbenzamide; or~~

~~N-cyclopropyl-3-fluoro-4-methyl-5-[3-methyl-1-(2-thienylsulfonyl)-1H-indazol-5-yl]benzamide~~; or a pharmaceutically acceptable salt thereof.

13. (cancelled)

14. (cancelled)

15. (withdrawn). A compound according to claim 1 which is:
N-[4-Methyl-3-(3-methyl-1,2-benzisoxazol-5-yl)phenyl]-2-pyrrolidin-1-ylisonicotinamide;

N-Cyclopropyl-3-[3-({[2-hydroxy-1-(hydroxymethyl)ethyl]amino}methyl)-1,2-benzisoxazol-6-yl]-4-methylbenzamide;

N-(3-Methoxyphenyl)-4-methyl-3-(3-piperidin-4-yl-1,2-benzisoxazol-6-yl)benzamide;

4-Methyl-3-(3-piperidin-4-yl-1,2-benzisoxazol-6-yl)-N-(1,3,4-thiadiazol-2-yl)benzamide;

N-[4-Methyl-3-(3-piperidin-4-yl-1,2-benzisoxazol-6-yl)phenyl]thiophene-3-carboxamide;

N-[4-Methyl-3-(3-piperidin-4-yl-1,2-benzisoxazol-6-yl)phenyl]-3-furamide;

N-(Cyclopropylmethyl)-4-methyl-3-(3-piperidin-4-yl-1,2-benzisoxazol-6-yl)benzamide;

or a pharmaceutically acceptable salt thereof.

16. (cancelled)

17. (withdrawn) A compound according to Claim 1 which is

4-Methyl-3-(3-piperidin-4-yl-1,2-benzisoxazol-6-yl)-N-(1,3-thiazol-2-yl)benzamide;

N-Cyclopropyl-4-methyl-3-[3-(1-piperazinyl)-1,2-benzisoxazol-6-yl]benzamide;

N-Cyclopropyl-4-methyl-3-[3-(4-morpholinyl)-1,2-benzisoxazol-6-yl]benzamide;

N-Cyclopropyl-4-methyl-3-{3-[2-oxo-2-(1-piperazinyl)ethyl]-1,2-benzisoxazol-6-yl}benzamide;

Methyl (6-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-1,2-benzisoxazol-3-yl)acetate;

N-Cyclopropyl-3-(3-{2-[(2-hydroxyethyl)amino]-2-oxoethyl}-1,2-benzisoxazol-6-yl)-4-methylbenzamide;

N-Cyclopropyl-4-methyl-3-{3-[2-oxo-2-(1-piperidinyl)ethyl]-1,2-benzisoxazol-6-yl}benzamide;

N-Cyclopropyl-4-methyl-3-{3-[2-(methylamino)-2-oxoethyl]-1,2-benzisoxazol-6-yl}benzamide;

N-Cyclopropyl-3-(3-{2-[(3-hydroxypropyl)amino]-2-oxoethyl}-1,2-benzisoxazol-6-yl)-4-methylbenzamide;

N-Cyclopropyl-3-(3-{2-[(cyclopropylmethyl)amino]-2-oxoethyl}-1,2-benzisoxazol-6-yl)-4-methylbenzamide;

N-Cyclopropyl-4-methyl-3-{3-[2-oxo-2-(1-pyrrolidinyl)ethyl]-1,2-benzisoxazol-6-yl}benzamide;

N-Cyclopropyl-3-{3-[2-(ethylamino)-2-oxoethyl]-1,2-benzisoxazol-6-yl}-4-methylbenzamide;

N-Cyclopropyl-3-{3-[2-(cyclopropylamino)-2-oxoethyl]-1,2-benzisoxazol-6-yl}-4-methylbenzamide;

N-Cyclopropyl-4-methyl-3-{3-[2-(4-morpholinyl)-2-oxoethyl]-1,2-benzisoxazol-6-yl}benzamide;

N-Cyclopropyl-4-methyl-3-{3-[2-({[3-(methyloxy)phenyl]methyl}amino)-2-oxoethyl]-1,2-benzisoxazol-6-yl}benzamide;

N-Cyclopropyl-4-methyl-3-{3-[2-oxo-2-(1,3-thiazol-2-ylamino)ethyl]-1,2-benzisoxazol-6-yl}benzamide;

N-Cyclopropyl-4-methyl-3-{3-[(4-methyl-1-piperazinyl)methyl]-1,2-benzisoxazol-6-yl}benzamide;

N-Cyclopropyl-4-methyl-3-[3-(1-piperidinylmethyl)-1,2-benzisoxazol-6-yl]benzamide;

N-Cyclopropyl-4-methyl-3-[3-(4-morpholinylmethyl)-1,2-benzisoxazol-6-yl]benzamide;

N-Cyclopropyl-4-methyl-3-[3-(1-pyrrolidinylmethyl)-1,2-benzisoxazol-6-yl]benzamide;

3-(3-Amino-1,2-benzisoxazol-6-yl)-N-cyclopropyl-4-methylbenzamide;

N-Cyclopropyl-3-[3-(cyclopropylamino)-1,2-benzisoxazol-6-yl]-5-fluoro-4-methylbenzamide;

6-{5-[(Cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}-N-(cyclopropylmethyl)-1,2-benzisoxazole-3-carboxamide;

6-{5-[(Cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}-N-propyl-1,2-benzisoxazole-3-carboxamide;

6-{5-[(Cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}-N-methyl-1,2-benzisoxazole-3-carboxamide;

6-{5-[(Cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}-N,N-dimethyl-1,2-benzisoxazole-3-carboxamide;

N-Cyclopropyl-6-{5-[(cyclopropylamino)carbonyl]-3-fluoro-2-methylphenyl}-1,2-benzisoxazole-3-carboxamide;

N-Cyclopropyl-3-fluoro-4-methyl-5-{1-[(4-methylphenyl)sulfonyl]-1H-indol-5-yl}benzamide;

N-Cyclopropyl-3-fluoro-4-methyl-5-[1-(phenylsulfonyl)-1H-indol-5-yl]benzamide;

N-Cyclopropyl-3-{2-[(cyclopropylcarbonyl)amino]-1,3-benzothiazol-6-yl}-4-methylbenzamide; or a pharmaceutically acceptable salt thereof.

18.(cancelled)

19. (cancelled)

20. (withdrawn) A pharmaceutical composition comprising a compound according to claim 6 in admixture with one or more pharmaceutically acceptable carriers, diluents or excipients.

21. (withdrawn) A pharmaceutical composition comprising a compound according to claim 12 in admixture with one or more pharmaceutically acceptable carriers, diluents or excipients.

22. (withdrawn) A pharmaceutical composition comprising a compound according to claim 15 in admixture with one or more pharmaceutically acceptable carriers, diluents or excipients.

23. (cancelled)

24. (withdrawn) A pharmaceutical composition comprising a compound according to claim 17 in admixture with one or more pharmaceutically acceptable carriers, diluents or excipients.

25. (cancelled)

26. (cancelled)

REMARKS

Claims 1 to 7, 10 to 12, 15, 17, 20-22, and 24 are in the application. Claims 8, 9, 13, 14, 16, 18, 19, 23, 25 and 26 have been cancelled. Claims 1, 2, 11 and 12 have been amended. Support for the amendments can be found in the specification on page 4, lines 27 to 32 and page 5, lines 1 to 3. Applicants reserve their right to file continuation or divisional applications on all cancelled or deleted subject matter.

The Examiner has held that Claims 13 to 26 have been provisionally withdrawn from consideration as non-elected subject matter. Applicants do not understand why claims 15 to 19 and their respective pharmaceutical composition claims have been held withdrawn. The subject matter of these claims were wholly contained within examined claim 6 and merely broken into four species claims as claims 6, and 15 to 19. Consequently, these claims and their respective additional composition claims should be examined together.

Obvious Double Patenting Rejection

Claims 1 to 5 and 7 to 11 are provisionally rejected under the judicially crated doctrine of obviousness-type double patenting as being unpatentable over Claims 1 to 13, 15, 16, and 18-22 of Applicants co-pending application USSN 10/587,790. Applicants respectfully traverse this rejection.

The Examiner comments that this rejection is being maintained as the pending claims are not allowable. This statement makes no sense relative to this rejection. Applicants instant application is the senior to Applicants copending application 10/587,790 (corresponding to that of WO 2005/073217). The USSN 10/587,790 application has a priority date of 30 January 2004. The present application has a priority date of 31 July 2002.

Without wishing to quote the entire MPEP sections regarding obvious type double patenting, specifically section 804, the Manuel is quite clear as to the process which should occur. In this instance the earlier-filed application (the instant one) should be permitted to issue as a patent without a terminal disclaimer. The later-filed application will be handled accordingly upon examination.

Consequently it is irrelevant to this rejection whether or not the claims in the instant case are "allowable" or not as the rejection is improper on its face. Withdrawal of the obviousness-type double patenting is requested.

Rejection under 35 USC §103

Claims 1 to 3, 5 and 7 to 11 are rejected under 35 USC§103(a) as being unpatentable over WO 2003/097610, Martina et al. Applicants respectfully traverse this rejection.

The Examiner comments that "[T]he '610 publication discloses several compounds which would anticipate Applicant's Markush language of Claim 1, with the exception that Applicant's instant genus must contain a methyl or chloro at the R1 position." See Page 5, lines 6 to 8 (Office Action).

The Pharmacia application discloses substituted indazole derivatives. Applicants A ring has been amended to further prosecution on the merits to several of the specifically identified rings in the specification, such as an isoxazolyl, pyrrolyl and thiazolyl rings. While the ring can be also be a pyrazolyl ring, this subject matter will be in a continuation application to be filed shortly.

The Pharmacia application does not teach nor suggest the fused isoxazolyl, pyrrolyl or thiazolyl rings as claimed herein. The Pharmacia application does not teach these specific rings also containing the required phenyl ring, attached in the 4-position of the fused bicyclo ring.

In view of these amendments and remarks, withdrawal of the rejection to the claims under 35 USC 103 is respectfully requested.

Rejection under 35 USC §112

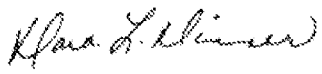
Claims 8 and 9 are rejected under 35 USC §112, first paragraph as being non enabling for treating "any condition or disease state mediated by p38 kinase activity in a patient" or "for treating any condition or disease stated mediated by cytokines produced by the activity of p38 kinase in a patient." Applicants respectfully traverse this rejection.

While Applicants do not agree with the Examiner that the specification is nonenabling for treatment of cytokine mediated diseases in order to further prosecution on the merits, the claims have been cancelled and will be filed in a continuation application for further prosecution.

Claims 6 and 12 were noted as being allowable but for the dependence on a rejected base claim. As it is believed that any rejections to the base claims have been overcome, all the claims in the application are believed to be in condition for allowance.

Should the Examiner have any questions or wish to discuss any aspect of this case, the Examiner is encouraged to call the undersigned at the number below. If any additional fees or charges are required by this paper the Commissioner is hereby authorized to charge Deposit account 19-2570 accordingly.

Respectfully submitted,



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IN THE UNITED STATES INTERNATIONAL EXAMINING AUTHORITY

Applicant:	Bamborough, et al.	4 April 2009
Serial No.:	10/587,790	Group Art Unit: 1614
Filed:	28 July 2006	Examiner: A. Pagonakis
Title:	FUSED HETEROARYL DERIVATIVES FOR USE AS P38 KINASE INHIBITORS	

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT

Sir:

Applicants now respond to the Office Action of 7 January 2009 for which entry of the following Remarks and Amendments into the record is respectfully requested.

Amendments to the Specification are reflected on page 2 of this paper.

Amendments to the Claims are reflected in the listing of claims which begins on page 3 of this paper.

Remarks begin on page 11 of this paper.

Amendments to the Specification

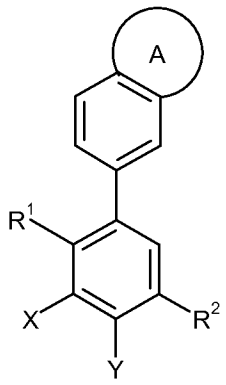
Page 1 under the title, please enter the following related application information:

This application is the §371 national stage entry of PCT/GB2005/000265, filed 27 January 2005.

Amendments to the claims

This listing of claims will replace all prior versions, and listings, of claims in the application:

1. (Currently Amended) A compound of formula (I):



(I)

wherein

A is a fused 5-membered heteroaryl ring substituted by -$(CH_2)_m$aryl or -$(CH_2)_m$heteroaryl wherein the aryl or heteroaryl is optionally substituted by one or more substituents independently selected from oxo, C_{1-6}alkyl, halogen, -CN, trifluoromethyl, -OR^3, -$(CH_2)_nCO_2R^3$, -NR^3R^4, -$(CH_2)_nCONR^3R^4$, -$NHCOR^3$, -$SO_2NR^3R^4$, _$NHSO_2R^3$ and -$S(O)_pR^3$, and

A is optionally further substituted by one substituent selected from -OR^5, halogen, trifluoromethyl, -CN, -CO_2R^5 and C_{1-6}alkyl optionally substituted by hydroxy;

R^1 is selected from methyl and chloro;

R^2 is selected from -NH-CO-R^6 and -CO-NH-$(CH_2)_q$-R^7;

R^3 is selected from hydrogen, -$(CH_2)_r$-C_{3-7}cycloalkyl, -$(CH_2)_r$heterocyclyl, -$(CH_2)_r$aryl, and C_{1-6}alkyl optionally substituted by up to two substituents independently selected from -OR^8 and -NR^8R^9,

R^4 is selected from hydrogen and C_{1-6}alkyl, or

R^3 and R^4, together with the nitrogen atom to which they are bound, form a 5-or 6-membered heterocyclic ring optionally containing one additional heteroatom selected from oxygen, sulfur and N-R^{10};

R^5 is selected from hydrogen and C_{1-6}alkyl;

R^6 is selected from hydrogen, C_{1-6}alkyl, -$(CH_2)_q$-C_{3-7}cycloalkyl, trifluoromethyl, -$(CH_2)_s$heteroaryl optionally substituted by R^{11} and/or R^{12}, and -$(CH_2)_s$phenyl optionally substituted by R^{11} and/or R^{12};

R^7 is selected from hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, -$CONHR^{13}$, phenyl optionally substituted by R^{11} and/or R^{12}, and heteroaryl optionally substituted by R^{11} and/or R^{12};

R^8 and R^9 are each independently selected from hydrogen and C_{1-6}alkyl;

R^{10} is selected from hydrogen and methyl;

R^{11} is selected from C_{1-6}alkyl, C_{1-6}alkoxy, -$(CH_2)_q$-C_{3-7}cycloalkyl, -$CONR^{13}R^{14}$, -$NHCOR^{14}$, halogen, -CN, -$(CH_2)_t NR^{15}R^{16}$, trifluoromethyl, phenyl optionally substituted by one or more R^{12} groups, and heteroaryl optionally substituted by one or more R^{12} groups;

R^{12} is selected from C_{1-6}alkyl, C_{1-6}alkoxy, halogen, trifluoromethyl, and -$(CH_2)_t NR^{15}R^{16}$;

R^{13} and R^{14} are each independently selected from hydrogen and C_{1-6}alkyl, or

R^{13} and R^{14}, together with the nitrogen atom to which they are bound, form a 5- or 6-membered heterocyclic ring optionally containing one additional heteroatom selected from oxygen, sulfur and N-R^{10}, wherein the ring may be substituted by up to two C_{1-6}alkyl groups;

R^{15} is selected from hydrogen, C_{1-6}alkyl and -$(CH_2)_q$-C_{3-7}cycloalkyl optionally substituted by C_{1-6}alkyl,

R^{16} is selected from hydrogen and C_{1-6}alkyl, or

R^{15} and R^{16}, together with the nitrogen atom to which they are bound, form a 5- or 6-membered heterocyclic ring optionally containing one additional heteroatom selected from oxygen, sulfur and N-R^{10};

X and Y are each independently selected from hydrogen, methyl and halogen;

m, n, p and q are each independently selected from 0, 1 and 2;

r and s are each independently selected from 0 and 1; and

t is selected from 0, 1, 2 and 3;

with the proviso that when A is substituted by -$(CH_2)_m$heteroaryl and m is 0, the -$(CH_2)_m$heteroaryl group is not a 5-membered heteroaryl ring optionally substituted by C_{1-2}alkyl;

or a pharmaceutically acceptable [[derivative]] salt thereof.

2. (Previously Presented) A compound according to claim 1 wherein A is a fused 5-membered heteroaryl ring containing up to two heteroatoms independently selected from oxygen and nitrogen.

3. (Previously Presented) A compound according to claim 1 wherein R^1 is methyl.

4. (Previously Presented) A compound according to claim 1 wherein R^2 is -CO-NH-$(CH_2)_q$-R^7.

5. (Previously Presented) A compound according to claim 1 wherein A is substituted by -$(CH_2)_m$heteroaryl wherein the heteroaryl is a 5- or 6-membered heteroaryl ring containing up to two heteroatoms independently selected from oxygen and nitrogen.

6. (Previously Presented) A compound according to claim 5 wherein the heteroaryl is optionally substituted by one or two substituents independently selected from oxo, C_{1-6}alkyl, halogen, -OR^3, -NR^3R^4 and -$(CH_2)_n$$CONR^3R^4$.

7. (Previously Presented) A compound according to claim 6 wherein the heteroaryl is substituted by one or two substituents independently selected from oxo and C_{1-6}alkyl.

8. (Previously Presented) A compound according to claim 1 wherein A is substituted by -$(CH_2)_m$aryl wherein the aryl is phenyl.

9. (Previously Presented) A compound according to claim 8 wherein the aryl is substituted by one or two substituents independently selected from C_{1-6}alkyl, halogen, -CN, trifluoromethyl, -OR^3, -NR^3R^4, -$(CH_2)_n$$CONR^3R^4$ and -$S(O)_pR^3$.

10. (Previously Presented) A compound according to claim 1 wherein X is hydrogen or fluorine.

11. (Currently Amended) A compound according to claim 1 substantially as hereinbefore defined with reference to any one of Examples 1 to 82, or a pharmaceutically acceptable [[derivative]] salt thereof.

12. (Currently Amended) A compound selected from:
N-cyclopropyl-3-fluoro-4-methyl-5-(1-phenyl-1*H*-indazol-5-yl)benzamide;
N-cyclopropyl-3-fluoro-5-[1-(4-fluorophenyl)-1*H*-indazol-5-yl]-4-methylbenzamide;

N-cyclopropyl-3-fluoro-5-[1-(4-fluoro-2-methylphenyl)-1*H*-indazol-5-yl]-4-methylbenzamide;

N-cyclopropyl-3-fluoro-4-methyl-5-{1-[4-(4-morpholinyl)phenyl]-1*H*-indazol-5-yl}benzamide;

N-ethyl-3-fluoro-4-methyl-5-(1-phenyl-1*H*-indazol-5-yl)benzamide;

N-(cyclopropylmethyl)-3-fluoro-4-methyl-5-(1-phenyl-1*H*-indazol-5-yl)benzamide;

N-cyclopropyl-3-fluoro-4-methyl-5-{1-[4-(methylsulfonyl)phenyl]-1*H*-indazol-5-yl}benzamide;

N-cyclopropyl-3-fluoro-4-methyl-5-(1-{4-[2-(methylamino)-2-oxoethyl]phenyl}-1*H*-indazol-5-yl)benzamide;

N-cyclopropyl-3-[1-(4-{[2-(dimethylamino)ethyl]amino}phenyl)-1*H*-indazol-5-yl]-5-fluoro-4-methylbenzamide;

N-cyclopropyl-3-fluoro-4-methyl-5-{1-[4-(tetrahydro-2*H*-pyran-4-ylamino)phenyl]-1*H*-indazol-5-yl}benzamide;

N-cyclopropyl-3-fluoro-4-methyl-5-(1-{4-[(tetrahydro-2-furanylmethyl)amino]phenyl}-1*H*-indazol-5-yl)benzamide;

N-cyclopropyl-3-(1-{4-[(2,3-dihydroxypropyl)amino]phenyl}-1*H*-indazol-5-yl)-5-fluoro-4-methylbenzamide;

N-cyclopropyl-3-fluoro-4-methyl-5-{1-[(1-oxido-2-pyridinyl)methyl]-1*H*-indazol-5-yl}benzamide;

N-ethyl-3-[3-(4-fluorophenyl)-1*H*-indazol-6-yl]-4-methylbenzamide;

N-cyclopropyl-3-[3-(4-fluorophenyl)-1*H*-indazol-6-yl]-4-methylbenzamide;

N-ethyl-4-methyl-3-{3-[4-(methyloxy)phenyl]-1*H*-indazol-6-yl}benzamide;

N-cyclopropyl-4-methyl-3-{3-[4-(methyloxy)phenyl]-1*H*-indazol-6-yl}benzamide;

N-(1-ethyl-1H-pyrazol-5-yl)-3-fluoro-5-[3-(4-fluorophenyl)-1H-indazol-6-yl]-4-methylbenzamide;

N-ethyl-3-fluoro-5-{3-[4-fluoro-2-(methyloxy)phenyl]-1H-indazol-6-yl}-4-methylbenzamide;

N-(1,4-dimethyl-1*H*-pyrazol-5-yl)-3-fluoro-5-[3-(4-fluorophenyl)-1*H*-indazol-6-yl]-4-methylbenzamide; [[and]]

N-(1,4-dimethyl-1*H*-pyrazol-5-yl)-3-[3-(4-fluorophenyl)-1*H*-indazol-6-yl]-4-methylbenzamide;

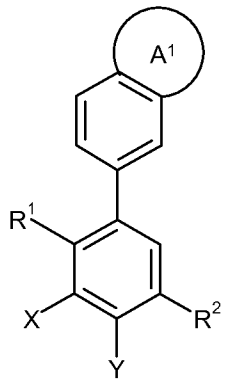
or a pharmaceutically acceptable [[derivative]] salt thereof.

13. (Currently Amended) A pharmaceutical composition comprising at least one compound according to claim 1, or a pharmaceutically acceptable [[derivative]] salt thereof, in association with one or more pharmaceutically acceptable excipients, diluents and/or carriers.

14. (Cancelled)
15. (Cancelled)
16. (Cancelled)
17. (Cancelled)

18. (Currently Amended/withdrawn) A process for preparing a compound of formula (I) according to claim 1, or a pharmaceutically acceptable [[derivative]] salt thereof, which comprises :

(a) reacting a compound of formula (II) :



(II)

in which R^1, R^2, X and Y are as defined in claim 1 and A^1 is an unsubstituted fused 5-membered heteroaryl ring with a halide derivative of formula (IIIA) or (IIIB) :

$$Z\text{-}(CH_2)_m aryl \quad \text{(IIIA)}$$

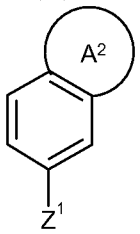
$$Z\text{-}(CH_2)_m heteroaryl \quad \text{(IIIB)}$$

in which $-(CH_2)_m$aryl and $-(CH_2)_m$heteroaryl are as defined in claim 1 and Z is halogen,
in [[the]] presence of a base,
or, when A is substituted by $-(CH_2)_m$aryl wherein m is 0, reacting the compound of formula (II) with a boronic acid compound of formula (IV)

$$(HO)_2B\text{-}(CH_2)_m aryl \quad \text{(IV)}$$

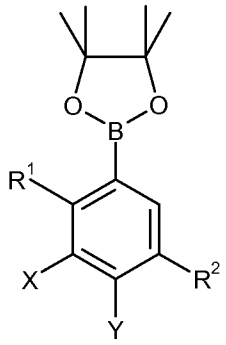
in which $-(CH_2)_m$aryl is as defined in claim 1[[,]] ;

(b) reacting a compound of formula (V):



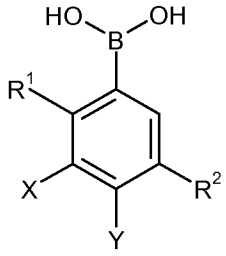
(V)

in which A^2 is A as defined in claim 1 and Z^1 is halogen,
with a compound of formula (VIA) or (VIB) :



(VIA)

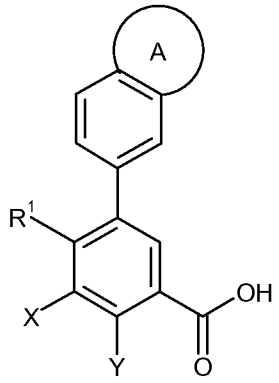
or



(VIB)

in which R^1, R^2, X and Y are as defined in claim 1,
in [[the]] presence of a catalyst;

(c) reacting a compound of formula (XVI) :



(XVI)

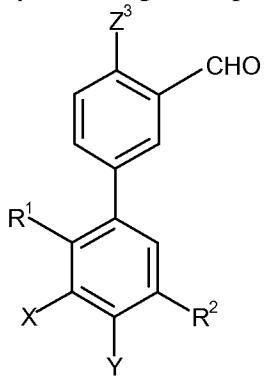
in which A, R^1, X and Y are as defined in claim 1,
with an amine compound of formula (XV) :

$$R^7\text{-}(CH_2)_q\text{-}NH_2$$

(XV)

in which R^7 and q are as defined in claim 1,
under amide forming conditions;

d) when A is a fused pyrazolyl, reacting a compound of formula (XVII) :



(XVII)

in which R^1, R^2, X and Y are as defined in claim 1 and Z^3 is halogen,
with a hydrazine derivative of formula (VIIIA) or (VIIIB) :

$$H_2NNH\text{-}(CH_2)_m\text{aryl}$$

(VIIIA)

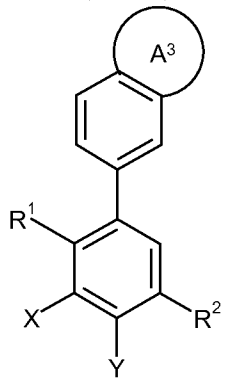
or

$$H_2NNH\text{-}(CH_2)_m\text{heteroaryl}$$

(VIIIB)

in which $-(CH_2)_m$aryl and $-(CH_2)_m$heteroaryl are as defined in claim 1;

(e) reacting a compound of formula (XVIII) :



(XVIII)

in which R^1, R^2, X and Y are as defined in claim 1 and A^3 is a fused 5-membered heteroaryl ring substituted by halogen, with a suitable boronic acid derivative; or

(f) final stage modification of one compound of formula (I) as defined in claim 1 to give another compound of formula (I) as defined in claim 1.

19 (Previously Presented). A compound according to claim 2 wherein R^1 is methyl.

20. (Previously Presented) A compound according to claim 2 wherein R^2 is -CO-NH-$(CH_2)_q$-R^7.

21. (Previously Presented) A compound according to claim 19 wherein R^2 is -CO-NH-$(CH_2)_q$-R^7.

22. (Currently Amended) A pharmaceutical composition comprising at least one compound according to claim 12, or a pharmaceutically acceptable [[derivative]] salt thereof, in association with one or more pharmaceutically acceptable excipients, diluents and/or carriers.

23. (Withdrawn) The compound according to Claim 1 which is:

N-cyclopropyl-3-fluoro-4-methyl-5-{3-[4-(methyloxy)phenyl]-1,2-benzisoxazol-6-yl}benzamide;

N-cyclopropyl-3-fluoro-5-[3-(4-hydroxyphenyl)-1,2-benzisoxazol-6-yl]-4-methylbenzamide; or

3-fluoro-5-[3-(4-fluorophenyl)-1H-indazol-6-yl]-4-methyl-N-(1-methyl-1H-pyrazol-5-yl)benzamide; or a pharmaceutically acceptable salt thereof.

REMARKS

Claims 1-13 and 19-23 are in the application. Claims 15, 16, 18 and 23 are withdrawn from consideration by the Examiner. Claims 1, 11-13, 18 and 22 are amended. Support for the amendment lies in the specification on page 7, lines 21 – 34. No new matter is believed added.

IDS/1449 Forms

The Examiner has attached with the Office Action, Applicants previously submitted 1449 forms. However, only Applicants 1449 forms submitted with the first "Information Disclosure Statement" (submitted 23 October 2008) has the accompanying PTOL 1449 forms completely signed. The Second IDS/1449 form, labeled as "Second Information Disclosure Statement" (also submitted 23 October 2008) only has the first page signed as being reviewed. Pages 2-5 of these 1449 forms are unsigned. Applicants respectfully request that the Examiner review the appropriate citations and return to Applicant the corresponding signed forms. If the Examiner requires any additional information or submittal by Applicant of new forms, please advise the undersigned at the number indicated below.

Restriction Requirement

Applicants respectfully request clarification with regard to the Examiner's comments on page 2 of the Office Action directed to the claims in the present application.

In summary, the claims of Group I of the October 17, 2008 Restriction Requirement are directed to a compound of Formula (I), in which claim 1 defines a Markush group, and Group III is directed to process claims, which are dependent on claim 1. Applicants respectfully point out that the Examiner may hold process claims withdrawn until the determination of patentable or allowable subject matter for the elected group, at which time rejoinder is possible. Based on the foregoing, as elected subject matter for examination on the merits is directed to a product (i.e., compound), Applicants now reserve the right to request rejoinder of commensurate in scope non-elected subject matter or inventions (i.e., such as corresponding treatment methods, pharmaceutical compositions and processes) upon the determination of allowable subject matter (*In re*

Ochiai, 71 F.3d 1565, 37 USPQ2d 1127 (Fed. Cir. 1995) and *In re Brouwer*, 77 F.3d 422, 37 USPQ2d 1663 (Fed. Cir. 1996); also see MPEP § 821.04 (b)).

Moreover, in the January 7, 2009 Office Action, the Examiner indicates that previously presented new claim 23 is withdrawn from consideration. Applicants respectfully disagree with the withdrawal of claim 23.

In particular, pending claim 23, which recites compound species that fall within the scope of claim 1 are properly included in restriction Group I directed to a compound of Formula (I) (i.e., support for claim 23 is found throughout the originally filed disclosure and in original claim 11 of the originally filed disclosure). As no art has been found to limit the scope of the claim 1, which defines a Markush group, the species defined in claim 23 should be examined as part of restriction Group I, directed to compounds of Formula (I).
Applicants request that the Examiner reconsider including claim 23 in restriction Group I for examination on the merits.

For the record, Applicants point out that as claims 14 and 17 were cancelled in the above-identified application, only claims 15 and 16 are to be considered as corresponding to non-elected Group II.

Based upon the foregoing, Applicants respectfully request that the Examiner consider above comments and remove the Finality of the Restriction Requirement as proper.

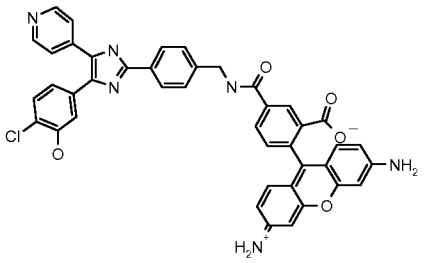
Priority
The present application is the §371 national stage entry of a Great Britain provisional application. While a reading of 37 CFR §1.78(a) and 35 CFR §365(c) is not believed to require such an amendment to the specification, Applicants have done so accordingly per the Examiners request.

Rejection under 35 USC §112, First Paragraph, Scope of Enablement

Claims 1-13, and 19-22 are rejected under 35 USC §112, first paragraph, as being enabling for the compounds of Formula (I), but not being enabling for "use of the same". Applicants respectfully traverse this rejection

The compounds claimed herein are all p38 kinase inhibitors. The specification clearly contains sufficient information on how to "use". See pages 22, lines 1 to 42 – page 32, lines 1 -11. In the Specification, pages 107, lines 35 to 41 – pages 110, lines 1 – 23 clearly teach suitable assays to determine activity. Contrary to the Examiner's assertion that the "Neither p38 kinase inhibition nor cessation of cell proliferation with the instantly claimed compounds has been demonstrated." (see Office Action Page 5, lines 5-6), activity for actual examples has been demonstrated therein. See page 110, lines 21 and 22 of the Specification. In fact, it should be noted that here is no requirement to provide actual data in the specification.

The Examiner comments that the "experimental protocols only mention the following compound:



and details a procedure on how to measure p38 kinase inhibition and how to determine whether cell proliferation has been halted". (See Office Action, Page 5, 1rst ¶).

The Examiner is correct that the compound above is mentioned therein. The compound is the fluorescent ligand used in the assay. It is not a compound of Formula (I), but used with a variable concentration of a compound of Formula (I) along with the p38 kinase enzyme. The specification actually discloses three variations of the Fluorescence kinase binding assay, which basically vary little on the volume of the testing liquid used.

The compounds of the Examples "were tested in at least one of these assays and had either IC_{50} values of <10 μM or pKi values of >6", as is shown on page 110, lines 22 and 23, as noted above. It should be noted that this is an art recognized assay for determining inhibitory activity of a compound against p38 kinase.

With respect to the state of the art at the time the application was filed, the signaling pathway of p38 kinase had been extensively studied. Applicants have previously provided on their IDS and 1449 forms additional information on the utility of p38 inhibitors for treatment of a wide range of diseases, including inflammation. It is well established in the art that there is a correlation of p38 inhibition and its affect on the pro-inflammatory cytokine cascade. Consequently, Applicants believe that they have provided sufficient grounds of enablement for the compounds of Formula (I) as described herein.

In particular the Examiner's attention is drawn to a previously submitted article on signalling cascades in inflammatory diseases (see Herlaar, E. et al., Molecular Med Today (1999), Vol. 5, 439-447). This article and other previously submitted articles on p38 kinase inhibitors detail the linkage to a number of acute and chronic inflammatory diseases, such as RA, osteoarthritis, inflammatory bowel disease, toxic shock syndrome, septic shock, asthma, chronic obstructive pulmonary disease (COPD), acute respiratory distress syndrome (ARDS), and osteoporosis. The skilled artisan would also be aware of the many more articles and work in the field which describes the role of pro-inflammatory cytokines in the diseases enumerated herein.

Applicants respectfully submit that the originally filed disclosure provides sufficient information on how to formulate, how to dose, and how to administer the compounds of Formula (I). Based on this, Applicants maintain that the specification is sufficiently enabled and would not require undue experimentation to practice the invention.

In the interests of advancing prosecution the method of use claims have been cancelled. Applicants reserve their right to continue prosecution on all cancelled subject matter in subsequent divisional or continuation application in accordance with U.S. Patent Practice.

In view of these remarks and amendments reconsideration and withdrawal of the rejection to the claims is respectfully requested.

Claims 1-13, and 19-22 are rejected under 35 USC §112, first paragraph, as being enabling for the compounds of Formula (I), but does not "reasonably provide enablement for derivatives of the compounds of Formula (I)". Applicants respectfully traverse this rejection.

As the term "pharmaceutically acceptable derivative" is defined in the specification on page 7, lines 21 to 31, the intended meaning of this term is clear based on the originally filed disclosure. In light of this, the skilled artisan would readily understand how to make a salt, solvate, ester, or a carbamate and/or phosphate ester of a compound of Formula (I).

However, in order to advance prosecution on the merits, Applicants have amended claims 1, 11-13, 18 and 22 to recite the phrase "pharmaceutically acceptable salt" as fully supported by the originally filed disclosure.

Rejection under 35 USC §112, First Paragraph, Written Description

Claims 1-13, and 19-22 are rejected under 35 USC §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey possession of the claimed invention. Applicants respectfully traverse this rejection.

The Examiner comments that the specification discloses "chemicals, such as compounds of formula I" which meet the written description and enablement for under 35 USC §112, first paragraph. (See Office Action, Page 12, lines 1-2, 2nd ¶). The Examiner then comments that claims 1-2, 4-6,9 and 18-20 are directed to encompass derivatives which only correspond in some undefined way to specifically instantly disclosed chemicals. None of these derivatives meet the written description provision due to "lacking chemical structural information for what they are".

Applicants are unclear as to what subject matter appears in claims 1-2, 4-6,9 and 18-20 that is not present in claims 3, 7, 8, 9-13, 19, 21 and 22? As noted above under the enablement rejection, the term "pharmaceutically acceptable derivative" is defined in the specification on page 7, lines 21 to 31, and reproduced below:

> "As used herein, the term "pharmaceutically acceptable derivative", means any pharmaceutically acceptable salt, solvate, or prodrug e.g. ester, of a compound of the invention, which upon administration to the recipient is capable of providing (directly or indirectly) a compound of the invention, or an active metabolite or residue thereof. Such derivatives are recognizable to those skilled in the art, without undue experimentation. Nevertheless, reference is made to the teaching of Burger's Medicinal Chemistry and Drug Discovery, 5th Edition, Vol 1: Principles and Practice, which is incorporated herein by reference to the

> extent of teaching such derivatives. Preferred pharmaceutically acceptable derivatives are salts, solvates, esters, carbamates and phosphate esters. Particularly preferred pharmaceutically acceptable derivatives are salts, solvates and esters. Most preferred pharmaceutically acceptable derivatives are salts and esters. "

The intended meaning of this term is clear based on the originally filed disclosure. In light of this teaching, the skilled artisan would readily understand how to make a salt, solvate, ester, or a carbamate and/or phosphate ester of a compound of Formula (I).

If the Examiner is commenting on a failure to meet the written description requirement of another term in Claims 1, 11, 12, 18 and 22 clarification is respectfully requested.

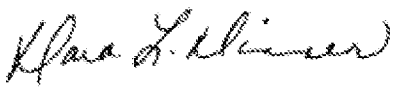
As Applicants have amended claims 1, 11-13, 18 and 22 to recite the phrase "pharmaceutically acceptable salt" as fully supported by the originally filed disclosure in place of "pharmaceutically acceptable derivative" (as supported on page 7, lines 14-20 and 32-43; and on page 8 lines 1-18) this rejection is believed to be rendered moot.

In view of these remarks and amendments reconsideration and withdrawal of the rejection to the claims is respectfully requested.

CONCLUSION

Should the Examiner have any questions or wish to discuss any aspect of this case, the Examiner is encouraged to call the undersigned at the number below. If any additional fees or charges are required by this paper, the Commissioner is hereby authorized to charge Deposit account 19-2570 accordingly.

Respectfully submitted,



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